Chapter 6

Palladium-catalyzed enantioselective conjugate addition of arylboronic acids to acyclic enones

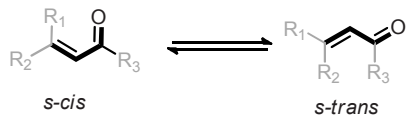
In this chapter, our study towards higher enantioselectivities in the palladium catalyzed conjugate addition of arylboronic acids to acyclic enones is discussed. The highest ee obtained was 77%. Yields of the isolated products were diminished, despite complete consumption of the starting material, due to a competing decomposition reaction.

Parts of this chapter will be submitted for publication: Gottumukkala, A. L., Matcha, K., de Vries, J. G., Minnaard, A. J., *Manuscript in preparation.*

6.1 Introduction

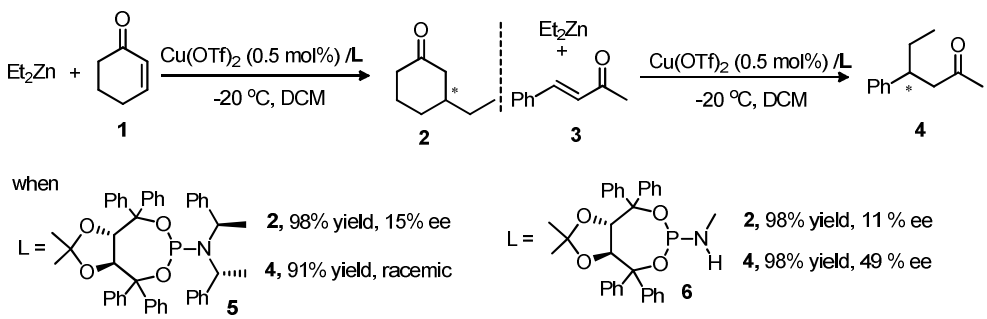
The transition metal catalyzed conjugate addition of organometallics to enones is an important tool for enantioselective carbon – carbon bond formation. The importance of this reaction in synthesis is clear from the extensive literature dedicated to this transformation.[1-4]

Acyclic enones are considerably more challenging substrates for conjugate addition reactions than cyclic enones, partly due to the existence of *s-cis* and *s-trans* conformers (Scheme 1).[1,5]



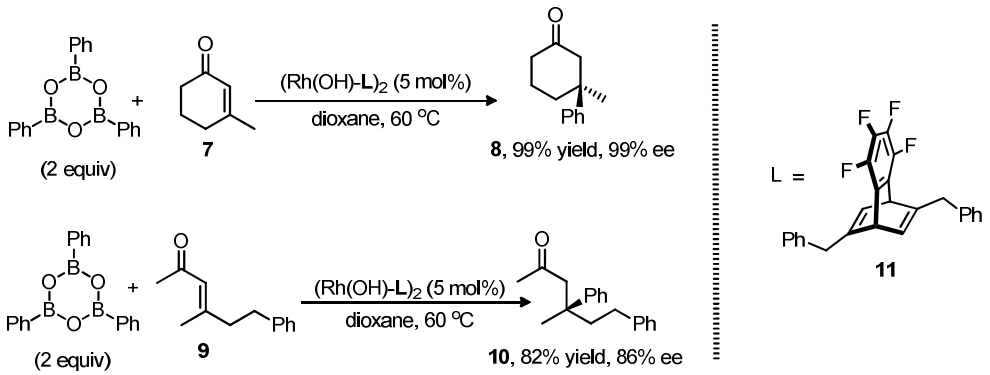
Scheme 1: *s-Cis* and *s-trans* conformations of enones.

As a result, very often, a different chiral ligand is necessary when compared to cyclic enones. For example, in the conjugate addition of organozinc reagents to cyclic and acyclic enones using a phosphoramidite ligand derived from TADDOL under similar reaction conditions,[5] a clear difference in enantioselectivity was observed (Scheme 2).



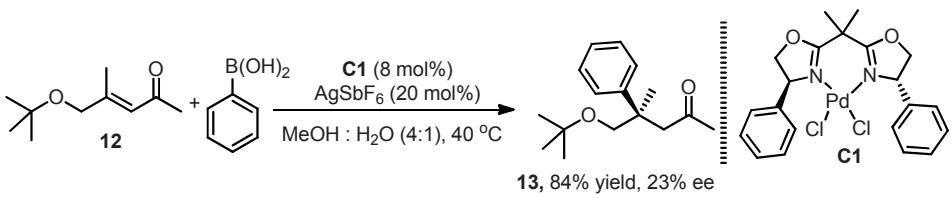
Scheme 2: Difference between cyclic and acyclic substrates in the Cu-catalyzed addition of diethylzinc.

Similarly, in an example of rhodium catalyzed conjugate addition of arylboroxines, acyclic substrates gave lower yields (82%) and enantioselectivities (86% ee) compared to cyclic enones (99% yield, and 99% ee), under identical conditions (Scheme 3).[6]



Scheme 3: Variation between cyclic and acyclic substrates in the Rh catalyzed addition of phenylboroxine.

Following the same trend, the conjugate addition of phenylboronic acid to **12** using $PdCl_2$-PhBOX gave only 23% ee (Scheme 4) as described in Chapter 4. The use of the bulkier TBDPS protecting group permitted an increase in ee (60%) but this was accompanied by the decomposition of the starting material and the formed product during the reaction.



Scheme 4: Conjugate addition of phenylboronic acid to 12 catalyzed by $PdCl_2$-PhBOX.

6.2 Goal

While the reaction above clearly demonstrates the applicability of Pd-catalyzed conjugate addition reactions to form quaternary centers in acyclic substrates, the selectivity obtained was much lower than in case of cyclic enones. Thus a detailed and separate study was necessary, to develop a set of reaction conditions necessary to obtain improved selectivity. We were interested in the development of a Pd-catalyzed conjugate addition of arylboronic acids to acyclic β,β-disubstituted enones, leading to the formation of benzylic quaternary centers with good enantioselectivity. Unlike cyclic enones, acyclic enones possess lesser structural rigidity.

6.3. Results and discussion

Based on our previous studies detailed in chapters 4 and 5, we surmised the following aspects.

1) Substrates bearing an allylic oxygen were necessary for the success of the reaction

2) New classes of chiral nitrogen ligands had to be assayed for the reaction.

Due to the limited commercial availability of chiral nitrogen ligands, it was decided to spend considerable effort in synthesizing several chiral nitrogen ligands for the reaction.

6.3.1 Synthesis of chiral nitrogen ligands

6.3.1.1 C_2–Symmetric chiral bipyridine ligands

Inspired by the success of bipyridine in conjugate addition reactions (Chapter 5) and the success of C_2 symmetric ligands in affording excellent enantioselectivities for cyclic substrates (Chapter 4), it was a natural choice to investigate the influence of chiral bipyridines (Figure 1). Chiral bipyridine ligands have been investigated in transition metal catalysis, and were found to be successful for a variety of reactions. Copper catalyzed allylic oxidation using ligand **15** provided the product in 82% ee (Scheme 5).[7]

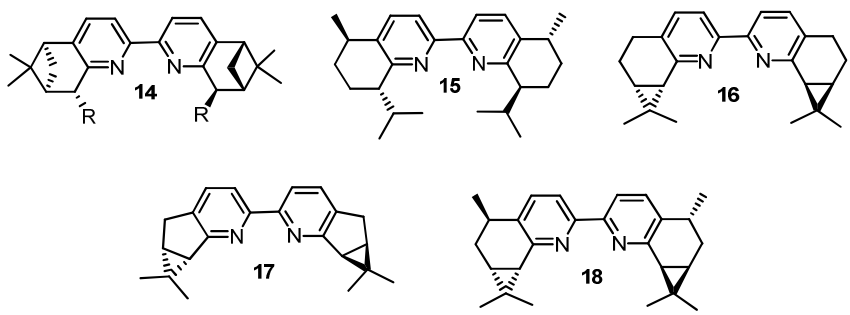
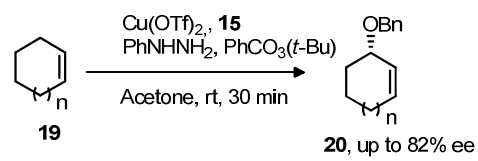


Figure 1: Chiral bipyridine ligands studied in transition metal catalysis.



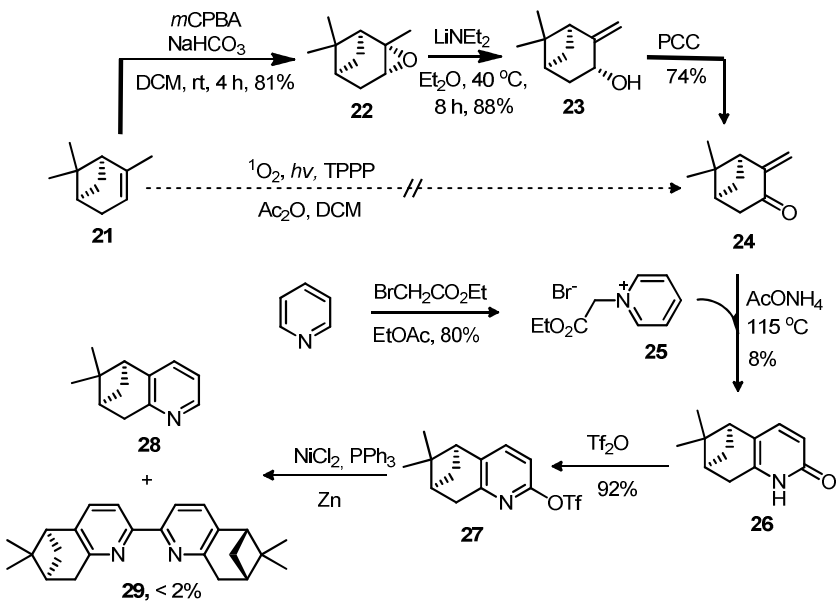
Scheme 5: Chiral bipyridine ligand 15 applied in Cu catalyzed allylic oxidation.[7]

6.3.1.2 Synthesis of *iso*-PINDY ligand

The synthesis of ligand **14** has been described by Kočovský[7] starting from (+)-α-pinene (Scheme 6). The first step of the reported synthesis is a singlet oxygen ene reaction, forming pinocarvone (–)-**24**. In our hands, this reaction remained difficult

to reproduce. This was perhaps due to the large size of the singlet oxygen apparatus (1 l) that was at our disposal, compared to the scale of the reaction we were working on (2 g). The stream of oxygen gas needed for the reaction, also led to the accelerated evaporation of the reaction mixture. Fortunately, we could overcome this shortcoming by an alternative route,[8] involving the epoxidation of **21**, followed by ring-opening with $LiNEt_2$ to form **23** and subsequent oxidation with PCC.

In our hands, the subsequent Kröhnke annulation[9,10] with pyridinium salt **25** proved to be particularly low yielding (8%). Using a recrystallized portion of **25** did not help. The subsequent triflation of **26** proceeded in 92% yield, the product of which was subjected to a nickel mediated Negishi-type coupling. The reaction remained incomplete even after 24 h (the reported yield after reaction overnight was 51%), and the majority of the product obtained was the hydrodetriflated product **28**. The expected homocoupled product **29** was obtained only trace quantities. Due to the difficulties experienced with the synthesis of **29** and the poor yields, it was decided to discontinue further efforts in this direction.

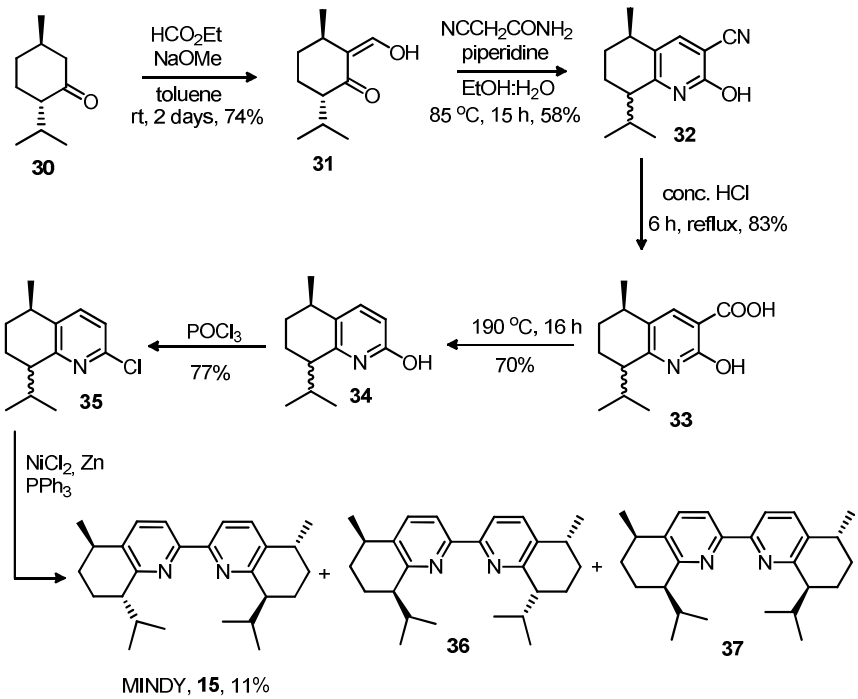


Scheme 6: Attempted synthesis of *iso*-PINDY ligand.

6.3.1.3 Synthesis of MINDY ligand

Next, we attempted the synthesis of MINDY (Scheme 7), a ligand derived from (–)-menthone (**30**). Claisen condensation of menthone with HCO_2Et afforded **31** in 74% yield, and subsequent Knoevenagel condensation with α-cyanoacetamide,

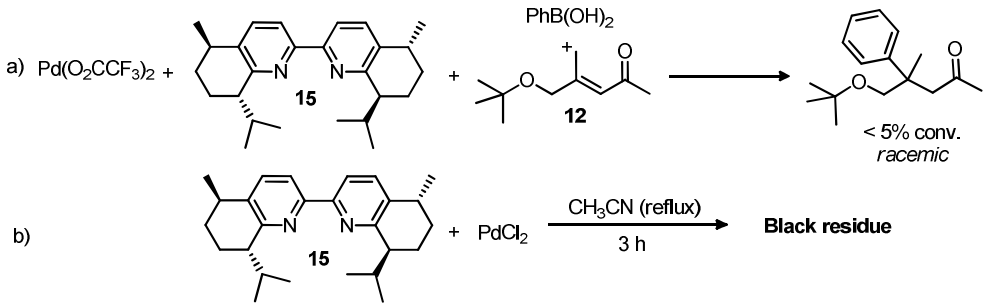
followed by spontaneous cyclization led to the formation of pyridine **32**. At this stage, however, a 1:1 mixture of epimers was obtained, which was carried forward in the synthesis. Acidic hydrolysis gave the hydroxy acid, which was subjected to pyrolytic decarboxylation, affording **34** in 70% yield. Next, chlorination of **34** with $POCl_3$ gave **35** in 77% yield, which was subjected to a nickel mediated dimerization. This led as expected to a mixture of diastereomers, which could be separated by column chromatography. The desired ligand **15** was isolated in only 11% yield.



Scheme 7: Synthesis of MINDY ligand.

15 Was tested in a conjugate addition reaction of phenylboronic acid to **12**, using the reaction conditions described in Chapter 5, for acyclic substrates (Scheme 8a). Disappointingly, the product was formed in only trace amounts, and found to be racemic. After several failed reactions, it was decided to verify the complexation of **15** with Pd. For this purpose, we attempted the complexation of **15** with $PdCl_2$ (Scheme 8b) as we had observed that $PdCl_2$ gave the corresponding Pd-complexes in good yields (Chapter 4). The reaction only resulted in a black residue which did not correspond to the product. Unfortunately, none of the added ligand could be recovered, or identified by ^{1}H-NMR, suggesting disintegration. Further, we tested if the residue obtained from the reaction was catalytically active, by adding

starting materials (**12** and phenylboronic acid) to the reaction. No reaction was observed.



Scheme 8: Attempted reactions with ligand 15.

The failure of complexation can perhaps be explained by the fact that the ligand is too sterically hindered for Pd. Spacefill models of **15**, generated using *Chem3D Pro®*, indeed indicate that the pyridine nitrogen is quite shielded by the bulky isopropyl group. In addition, in its energetically most stable conformation the molecule probably adopts a conformation wherein the two nitrogens are "*trans*" to one another (Figure 2), thereby making complexation difficult.

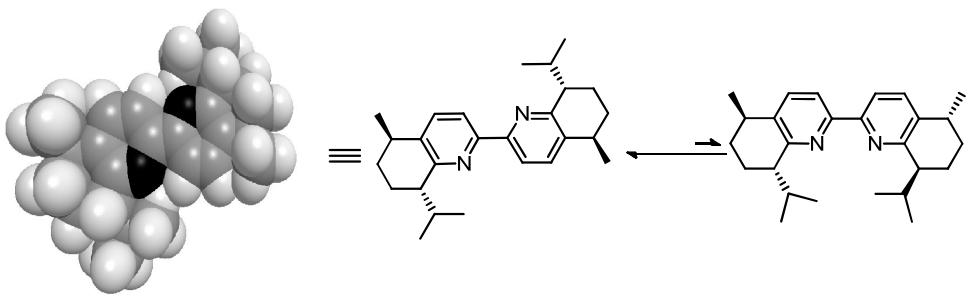


Figure 2: Conformations of ligand 15.

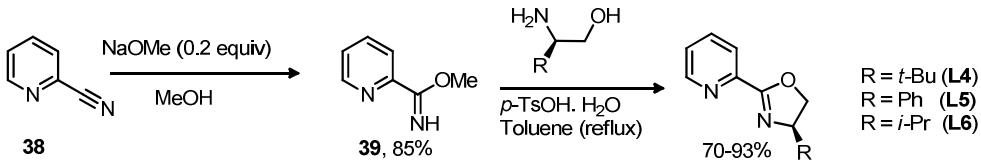
Taking these failures with C_2 symmetric ligands into account, it was decided to study C_1-symmetric ligands. Our decision in this direction was further leveraged by the report of Stoltz,[11] wherein excellent enantioselectivities for cyclic substrates were obtained using a C_1 symmetric ligand.

6.3.2 Synthesis of C_1–symmetric ligands

Learning from the good selectivities obtained using oxazoline based ligands[12] (Chapter 4), we decided to continue with this class of ligands. Candidates that were not available commercially had to be synthesized, however.

6.3.2.1 C_1–symmetric chiral pyridyl oxazolines

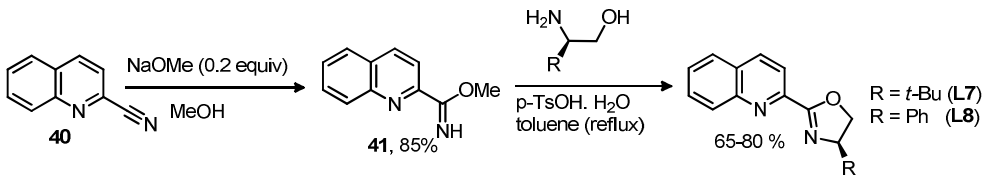
Learning from the work of Stoltz,[11] we went on to prepare a set of pyridyl-oxazolines (**L4**-**L6**), using various amino acids. Their two step synthesis is described in Scheme 9. These ligands were then used in catalysis.



Scheme 9: Synthesis of pyridyl-oxazoline ligands.

6.2.2.2 C_1–symmetric chiral quinoline-oxazolines.

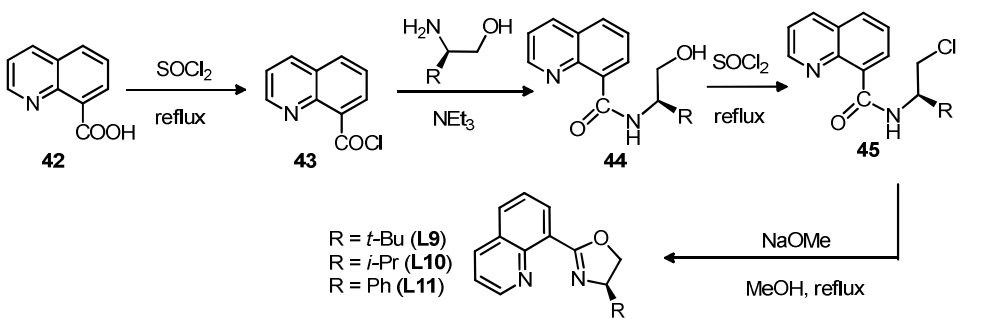
Pd^{II}-complexes of chiral quinoline-oxazolines have been found to be excellent catalysts for enantioselective oxidative cascade cyclizations[13] and aza-Wacker-type cyclizations of olefinic tosylamides.[14] The synthesis of these ligands proceeds similar to ligands **L4**-**L6** (Scheme 10), when starting from quinoline-2-nitrile (**40)**



Scheme 10: Synthesis of quinolone-oxazoline ligands.

6.3.2.3 C_1–symmetric chiral quinolinyl-oxazolines

Furthermore, we proceeded to synthesize a set of C_1 symmetric quinolinyl-oxazolines. This class of ligands has been found to be effective in the Pd catalyzed asymmetric hydroarylation of norbornenes.[15] The synthesis proceeded starting from 8-quinolinecarboxylic acid **42** as presented in scheme 11.



Scheme 11: Synthesis of quinolinyl-oxazoline ligands.

6.3.3 Optimization of reaction parameters.

With the synthesized ligands and complexes in hand (Figure 3), the Pd-catalyzed conjugate addition reaction of phenylboronic acid to **12** was tested. The results are summarized in Table 1. As noted previously (Chapter 5, section 5.3.3), acyclic enones, in general, required longer reaction times and higher reaction temperatures (80 ^{o}C) to reach full conversion. Hereinafter, 3 equiv of the phenylboronic acid was necessary to afford full conversion, while only 1.5 equiv was necessary in the case of cyclic substrates (Chapter 4). This could be due to increased protodeboronation of the arylboronic acids at elevated temperatures.[16]

Picking up from the success of bisoxazoline ligands in the conjugate addition reaction to cyclic enones, we started our screening program with the optimized conditions (Table 1, entry 1) reported in Chapter 4. The starting material was fully consumed (as measured by GC) during the reaction, although the product was formed in only 24% ee. Retaining the ligand and using $Pd(O_2CCF_3)_2$ as the Pd precursor, resulted in a diminished conversion, while maintaining the same ee (entry 2). Bulkier *tert*-butyl substituents on the ligand led to poor performance (entry 3) in the reaction. A similar fate was shared by ligand **L3** (entry 4) and its corresponding complex **C2** (entry 5). In the latter case, upon dehalogenation it is likely that a C-H activation of the proximal *iso*-propyl group by the dicationic palladium results in the deactivation of the catalyst.[17] Ligand **L4** was tested under the conditions described by Stoltz,[11] which led to an improved 34% ee, though conversion was incomplete (entry 6). Learning from the work of Stoltz, we opted for DCE as a solvent, in view of the higher reaction temperature. The addition of 20 vol% water along with $KSbF_6$ resulted in full conversion (entry 7). The beneficial influence of the water could be due to improved transmetalation.[18] The role of SbF_6^- in improving conversions has been discussed before (Chapter 4, section 4.3.1). The use of other ligands from the same class (**L5**, **L6**) only resulted in poorer results (entries 8, 9). Complex **C3**, synthesized from ligand **L4**, however demonstrated an improved ee (entry 10) and full conversion. Use of quinoline-oxazolines **L7** and **L8** led to full conversion, although lower ee's were obtained (entries 11,12). Use of **L7** derived **C4** also resulted in full conversion, although the ee obtained was only 42%. Application of *tert*-butyl bearing quinolinyl-oxazoline **L9** induced 33% ee, while ligand **L11** afforded an impressive 69% ee. Complex **C5** derived from **L11** also afforded full conversion with 71% ee.

P,N-ligands **L12** and **L13** induced very high ee's (entries 18, 19), but the conversions remained low. Finally, we tried the Spirobox class of ligands **L14** and **L15**, which only resulted in trace amounts of product being formed.

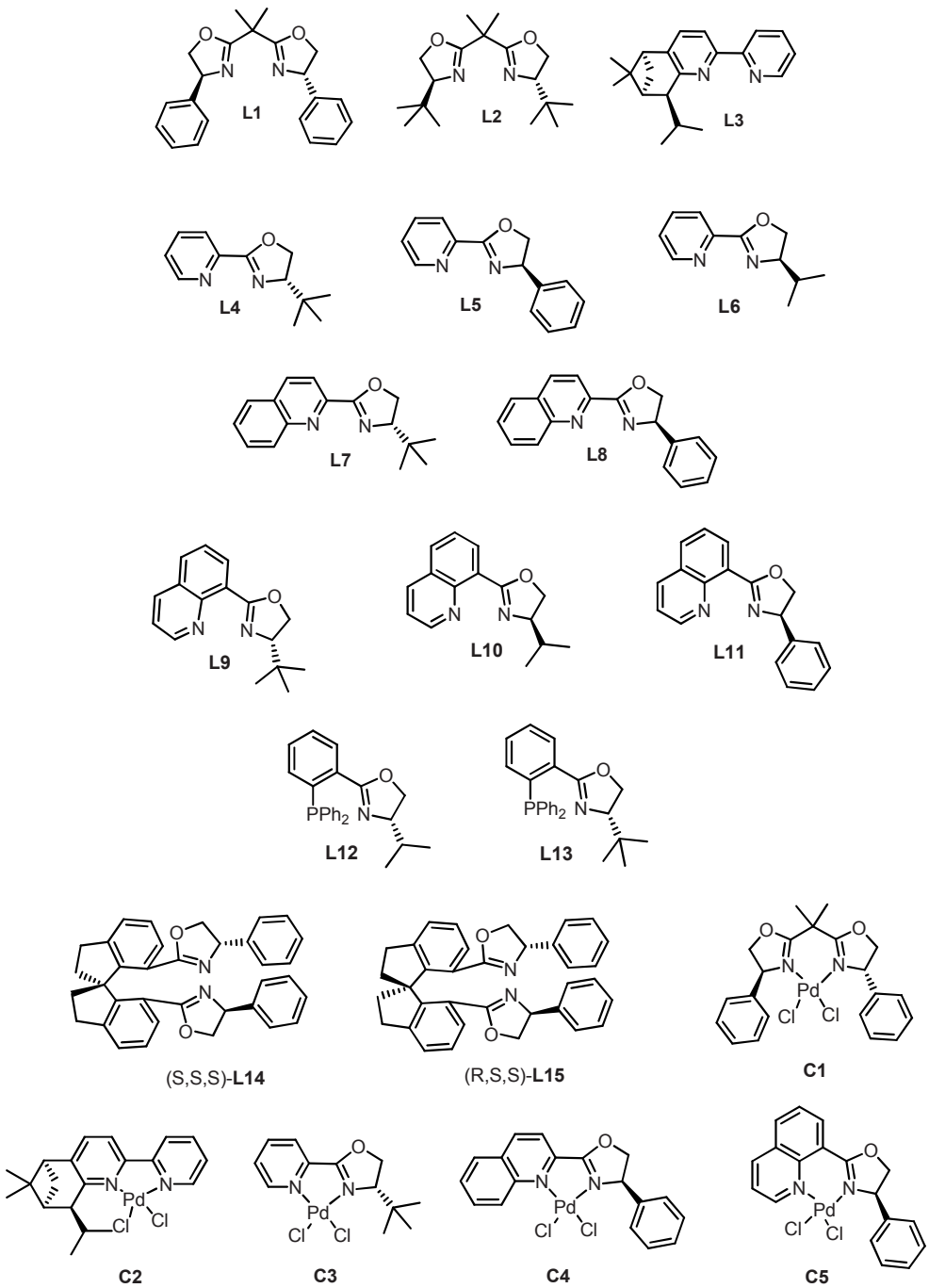
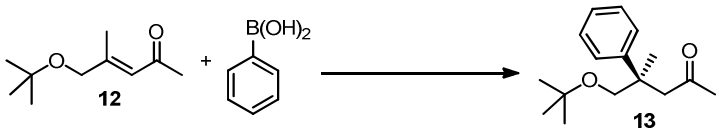


Figure 3: Ligands and complexes used for the optimization studies

Table 1: Optimization of reaction parameters for the conjugate addition of phenylboronic acid.[a]



Entry	Pd	Ligand	Solvent	Additive	Conv[b]	ee[c]
1	**C1**	-	MeOH:H_2O	$AgSbF_6$	full	24
2	$Pd(O_2CCF_3)_2$	L1	MeOH:H_2O	-	65	25
3	$Pd(O_2CCF_3)_2$	L2	MeOH:H_2O	-	< 2	nd
4	$Pd(O_2CCF_3)_2$	L3	MeOH:H_2O		-	nd
5	**C2**	-	MeOH:H_2O	$AgSbF_6$	-	nd
6	$Pd(O_2CCF_3)_2$	L4	DCE	-	87	34
7	$Pd(O_2CCF_3)_2$	L4	DCE:H_2O	$KSbF_6$	full	35
8	$Pd(O_2CCF_3)_2$	L5	DCE:H_2O	$KSbF_6$	full	11
9	$Pd(O_2CCF_3)_2$	L6	DCE:H_2O	$KSbF_6$	full	6
10	**C3**	-	MeOH:H_2O	$AgSbF_6$	full	54
11	$Pd(O_2CCF_3)_2$	L7	DCE:H_2O	$KSbF_6$	full	33
12	$Pd(O_2CCF_3)_2$	L8	DCE:H_2O	$KSbF_6$	full	38
13	**C4**	-	MeOH:H_2O	$AgSbF_6$	full	42
14	$Pd(O_2CCF_3)_2$	L9	DCE:H_2O	$KSbF_6$	78	33
15	$Pd(O_2CCF_3)_2$	L10	DCE:H_2O	$KSbF_6$	full	56
16	**$Pd(O_2CCF_3)_2$**	**L11**	**DCE:H_2O**	**$KSbF_6$**	**full**	**69**
17	**C5**	-	MeOH:H_2O	$AgSbF_6$	full	71
18	$Pd(O_2CCF_3)_2$	L12	DCE:H_2O	$KSbF_6$	31	89
19	$Pd(O_2CCF_3)_2$	L13	DCE:H_2O	$KSbF_6$	26	91
20	$Pd(O_2CCF_3)_2$	L14	DCE:H_2O	$KSbF_6$	<10	nd
21	$Pd(O_2CCF_3)_2$	L15	DCE:H_2O	$KSbF_6$	<10	nd

[a] **12** (0.2 mmol, 1 equiv), phenylboronic acid (0.6 mmol, 3 equiv) Pd precursor or Pd complex (5 mol%), ligand (7 mol%), additive (20 mol%), solvent : H_2O (4:1) 0.5 ml, 18 h, 80 °C [b] Conversion determined by

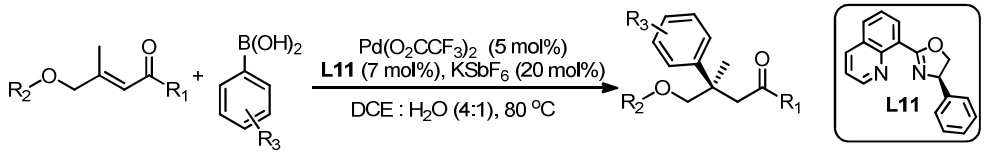
GC analysis of reaction mixture. [c] ee determined by chiral HPLC analysis of the isolated product [chiralpak OJ-H, *n*-heptane : *i*-PrOH (99:1), 210 nm]. DCE = 1,2-dichloroethane, nd = Not determined.

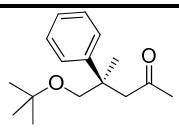
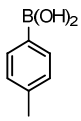
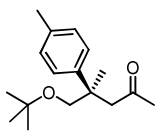
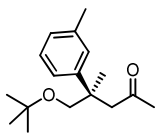
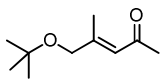
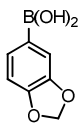
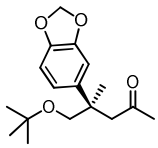
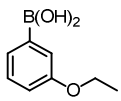
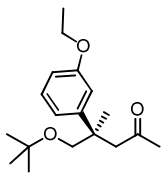
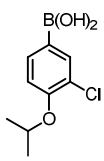
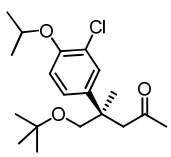
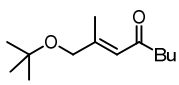
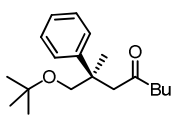
From the above set of experiments, we learned that ligand **L11** afforded the best ee's, along with full conversion. Realizing that the difference in ee when using $Pd(O_2CCF_3)_2$ / **L11** and complex **C5** was marginal, we decided to use the former for further experimentation, in view of convenience.

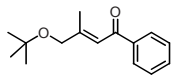
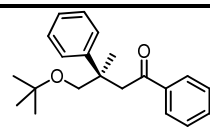
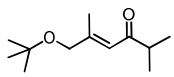
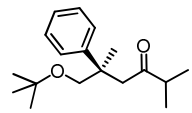
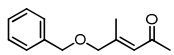
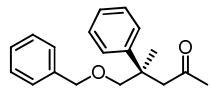
6.3.4 Substrate scope of the reaction

With the optimized conditions in hand, we proceeded to study the scope of the reaction. The results are summarized in Table 2. The conjugate addition of phenylboronic acid to **12**, gave **13** in 71% yield and 69% ee. With *p*-tolylboronic acid, **13b** was obtained in 74% yield, with a minor drop in ee to 65%. Use of *m*-tolylboronic acid gave **13c** gave the product in 70% yield and 64% ee. Reaction with alkoxy-substituted boronic acids, gave the corresponding products **13d** and **13e** in a reduced yield of 42% and 53%, respectively. The ee in these cases was 59% and 57%, respectively. Interestingly, when a chloro-substituted alkoxyboronic acid was used, the yield and ee improved, affording **13f** in 83% yield and 77% ee. Substrate **46**, bearing a butyl chain, was arylated to give the corresponding product **47** in 71% ee. Phenyl containing substrate **48,** afforded **49** with similar selectivity (69%). Comparing entries 1, 7, 8 and 9, it is concluded that the substituent on the α- position of the carbonyl, does not have an significant influence on the ee of the formed product. Substrate **52** bearing a benzyl substituent also afforded the expected conjugate addition product (**53**) in 63% yield and 71% ee.

Table 2: Substrate scope with a variety of enones.[a]



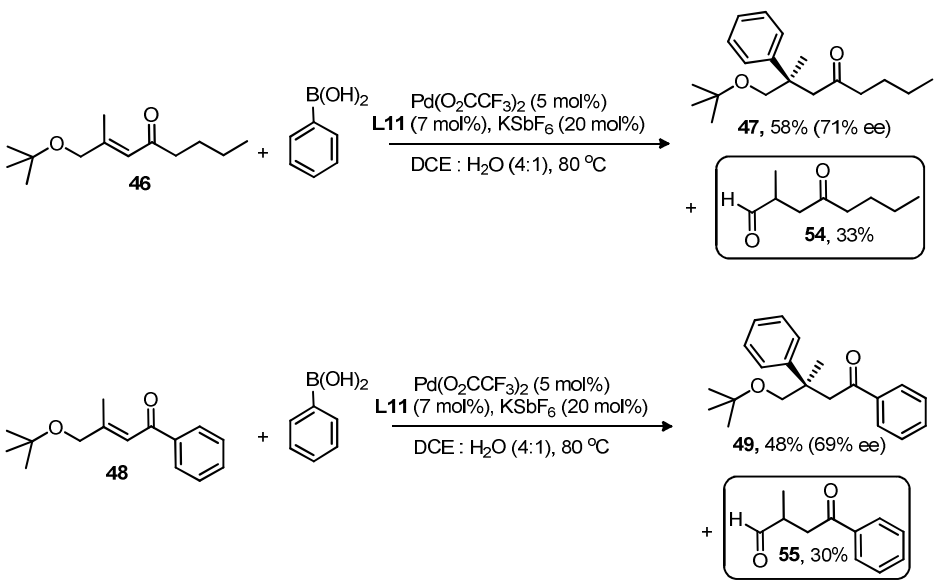
Entry	Substrate	Boronic Acid	Product (yield[b])	ee[c] (%)
1			 **13** (71)	69
2			 **13b** (74)	65
3			 **13c** (70)	64
4	 **12**		 **13d** (42)	59
5			 **13e** (53)	57
6			 **13f** (83)	77
7	 **46**		 **47** (58)	71

Entry	Substrate	Boronic Acid	Product (yield)	ee (%)[C]
8	 **48**		 **49** (48)	69
9	 **50**		 **51** (32)	71
10	 **52**		 **53** (63)	71

[a] enone (0.5 mmol, 1.equiv), phenylboronic acid (1.5 mmol, 3 equiv) $Pd(O_2CCF_3)_2$ (8.3 mg, 5 mol%), **L11** (9.6 mg, 7 mol%), $KSbF_6$ (27 mg, 20 mol%), DCE : H_2O (4:1) 1 ml, 18h. 80 °C. [b] Isolated yield. [c] ee determined by chiral HPLC analysis of the isolated product.

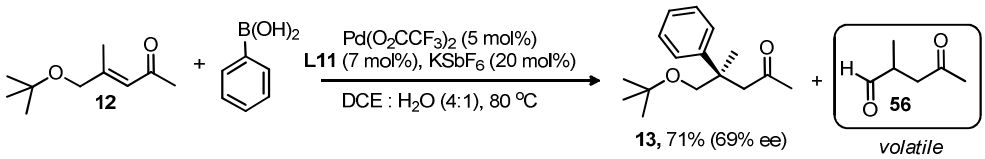
6.3.5 Substrate decomposition

Examining Table 2, it is apparent that the isolated yields of the products are essentially in the range of 65-75%, despite the starting material being consumed completely in the reaction. This remained a puzzle until substrate **46** and **48** were tested in the conjugate addition reaction. In addition to the expected conjugate addition product, we also observed the formation of a keto-aldehyde (**54**, **55**) as side product (Scheme 12). **54** and **55** could be isolated and characterized.



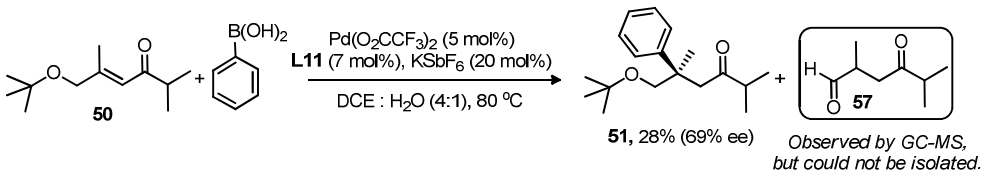
Scheme 12: Side products obtained from the reaction.

By analogy, one might expect that such a side product (**56**) might even be formed in the case of substrate **12**. However, **56** is of low molecular weight, and expected to be quite volatile. Consequently, it escapes detection by GC/MS or crude ^{1}H-NMR of the reaction mixture. The formation of **56** might account for the "missing yield" of **13** (Scheme 13).



Scheme 13: Side product could not be detected.

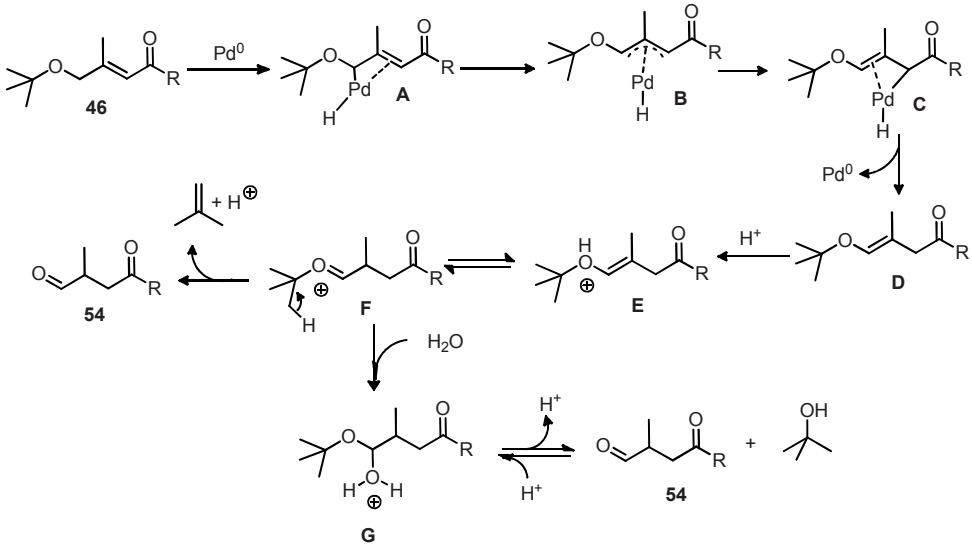
This hypothesis is further confirmed by the formation of ketoaldehyde **57**, formed in the reaction of **50**, which was observed by GC-MS, but could not be isolated (Scheme 14).



Scheme 14: Side product detected by GC/MS.

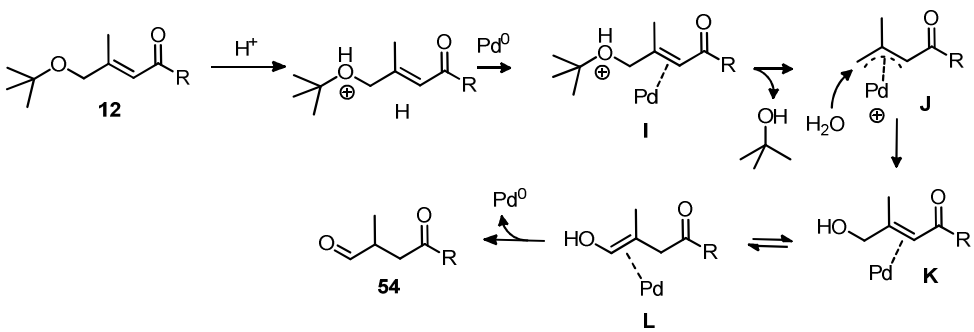
Two plausible mechanisms are proposed for the formation of the ketoaldehyde side product (Scheme 15, 16). Both mechanisms invoke a Pd allyl species (**B** and **J**) that is formed by an oxidative addition to Pd^0 species. It must be emphasized that at this time, both mechanisms are speculative, and due to time constraints no experimental data has been collected to prove or disprove these mechanisms.

Considering the mechanism presented in Scheme 15, a sequence involving oxidative addition of Pd^0, π-allyl formation (**B**), and reductive elimination liberating Pd^0 is proposed to explain the isomerization of the double bond, leading to the formation of **D**. Since phenylboronic acid is a weak acid (pK_a of 8.9 in water, comparable to phenol),[16] one might expect that it protonates the enol ether, forming species **E** and **F**. These can expel isobutene and form the observed product **54**. Alternatively, **F** can undergo hydrolysis via hemi-acetal **G**, to give **54** and *tert*-butanol. A weak point of this hypothesis is that **D** has not been observed in the reaction.



Scheme 15: Plausible mechanism for the formation of 54.

An alternative pathway involves a *"Tsuji-Trost type"* mechanism, in which an allyl species is formed by expelling (protonated) *tert*-butanol (**J**), followed by nucleophillic attack of water to form **K**. This then isomerizes to **L**, as shown in Scheme 16. Tautomerization of **L** gives **54**. Although **K** was not observed as such in the reactions, we did observe such deprotection (especially incases of substrates bearing silyl protecting groups) and hemiacetal formation, in an earlier phase of the research (Chapter 4, section 4.3.2).



Scheme 16: Plausible formation of side-product 54 via a *Tsuji-Trost type* pathway.

Control experiments performed in the absence of Pd did not afford the ketoaldehydes. Since the catalyst employed for the reaction is chiral, it is possible that the formed ketoaldehyde is enantiomerically enriched. However, **54** and **55** did not show any optical activity in a polarimeter. This could also be explained by the rapid racemization of the stereocenter next to the aldehyde via keto-enol

tautomerism, under the acidic conditions of the reaction or alternatively, that they are indeed enantioenriched but their specific rotation is extremely low. Further studies, could focus on the synthesis of the racemate for comparison.

6.4 Summary and conclusions

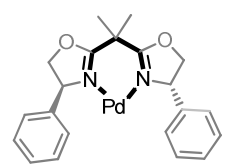
In this chapter, we describe the first examples of Pd catalyzed enantioselective conjugate addition of arylboronic acids to β,β-disubstituted linear enones. Enantioselectivities up to 77% could be achieved for a series of substrates bearing an allylic oxygen. Substituting the methyl group of substrate **12** with an *n*-butyl or phenyl did not seem to have an influence on the enantioselectivity of the formed product.

Though the ee's obtained are considerably lower than those obtained with cyclic enones, these represent the first examples. The isolated yield of the products was mostly in the range of 60-70% despite the substrates being completely consumed in the reaction. The "missing yield" could be accounted for by competing Pd-catalyzed decomposition of the substrate.

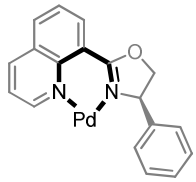
6.5 Future perspectives

Future studies should include a mechanistic elucidation of the formation of the side product, leading to changes in the catalyst system to arrest its formation. In addition, design and study of new ligands is desirable, to increase the enantioselectivity.

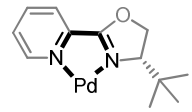
While examining the most successful ligands for conjugate addition to acyclic substrates from the current chapter (**L11**) and cyclic substrates described in chapter 4 (**L1**), it might be interesting to note that both these ligands form a 6-membered palladacycle (Figure 3). On the other hand, ligand **L4**, reported by Stoltz,[11] forms a 5-membered cycle, and led to lower enantioselectivities compared to **L1** for cyclic substrates and **L11** for acyclic substrates The 6-membered cycle might allow the stereodirecting element in oxazole to be closer to the metal center, thus affording higher enantioselectivities. Thus, future development could focus on the design of more ligands bearing 6-membered palladacycles, and with increased steric bulk of the stereodirecting element of the ligand. Plausible structures are presented in Figure 4.



L1, 6 - membered cycle

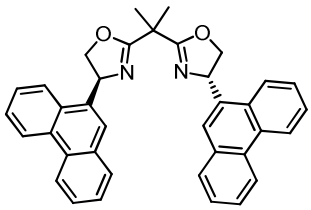


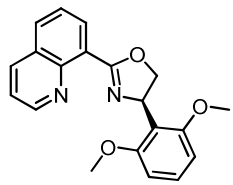
L11, 6 - membered cycle



L4, 5 - membered cycle

Figure 3: Palladacycles formed from the ligands L1, L4 and L11.





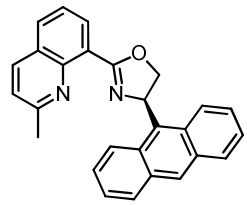


Figure 4: Plausible ligand designs for improved enantioselectivity.

6.6 Experimental

6.6.1 General

All experiments were carried out in flame dried or oven dried (150 ^{o}C) glassware, in an atmosphere of dinitrogen, unless specified otherwise, by standard Schlenk techniques. Schlenk reaction tubes with screw caps, and equipped with a teflon-coated magnetic stir bar were flame dried under vacuum and allowed to return to room temperature prior to being charged with reactants. A manifold permitting switching between dinitrogen atmosphere and vacuum was used to control the atmosphere in the reaction vessel. Reaction temperature refers to the temperature of the oil bath.

Flash chromatography was performed using Merck silica gel type 9385 (230-400 mesh), using the indicated solvents. All solvents used for filtration and chromatography were of commercial grade, and used without further purification. Anhydrous methanol, and acetonitrile were sourced from Sigma-Aldrich or Acros and stored under dinitrogen.

TLC was performed on Merck silica gel 60, 0.25 mm plates and visualization was done by UV and staining with Seebach's reagent (a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H_2O (500 ml) and H_2SO_4 (25 ml)) or Vanillin Stain (a mixture of vanillin (6g), conc. sulphuric acid (1.5 ml) and ethanol (95 ml)) or $KMnO_4$ stain.

^{1}H- and ^{13}C-NMR were recorded on a Varian AMX400 (400, 100.59 MHz, respectively) using $CDCl_3$ as solvent, unless specified otherwise. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: δ 7.27 for ^{1}H, δ 77.1 for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants *J* (Hz), and integration.

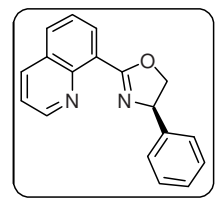
GC-MS measurements were made using a HP 6890 Series Gas Chromatograph system equipped with a HP 5973 Mass Sensitive Detector. GC measurements were made using a Shimadzu GC 2014 gas chromatograph system bearing a AT5 column (Grace Alltech) and FID detection. Whenever GC conversion is reported,

the quantification was done using cyclo-octane as internal standard. High Resolution Mass Spectrometry was performed using a ThermoScientific LTQ Oribitrap XL spectrometer.

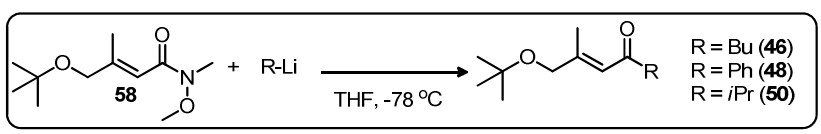
The absolute configuration of the products described herein is not known.

Synthesis of starting materials: Synthesis of substrates **12** and **52** has been described earlier (Chapter 4, Section 4.5). **15,**[7,19] **27,**[7,19] **L4,**[11] **L5,**[20] **L6,**[20] **L7,**[13] **L8,**[21] **L9,**[15]**, L10,**[22] **L11,**[22] and **C4**[13] were synthesized according to literature procedures. Ligands **L12**, **L13**, **L14** and **L15** were obtained commercially.

Ligand **(*R*)-L11** was synthesized according to literature procedure.[22] The absolute configuration was assigned by comparing the sign of the optical rotation.[21] $[\alpha]_{20}^{D}$= +22.1° ($CHCl_3$, *c* 3). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.09 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.24 (dd, *J* = 6.9, 1.5 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.95 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.20–7.55 (m, 6H), 5.57 (dd, *J* = 10.2, 8.1 Hz, 1H), 4.97 (dd, *J* = 10.2, 1.7 Hz, 1H), 4.45 (t, *J* = 8.3 Hz, 1H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 165.2, 151.3, 146.2, 142.6, 136.3, 131.9, 131.2, 128.7, 128.4, 127.9, 127.5, 126.9, 125.8, 121.4, 75.3, 70.4.



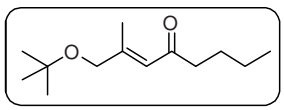
46, **48** and **50** were synthesized as described below, starting from **58** (Chapter 4, Section 4.5).



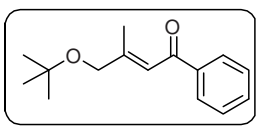
To a solution of **58** (1 mmol, 523 mg, 1 equiv) in dry MTBE (20 ml) at –78 °C, was added an ethereal solution of the organolithium reagent (1.3 equiv), dropwise via a syringe over 30 min. Following addition, the reaction was allowed to stir at this temperature, till complete consumption of **58** (45 min – 2 h). Upon completion, the reaction was quenched by dropwise addition of saturated aqueous NH_4Cl, and allowed to warm to rt. The reaction was diluted with diethylether (25 ml), and stirred till a clear phase separation occurred upon arresting the stirring. The organic layer was separated, washed with water (2 X 20 ml) and brine (2 X 10 ml), dried over

anhydrous $MgSO_4$, and concentrated. The concentrate was loaded directly onto a silica gel column and eluted with a *n*-pentane : diethylether mixture.

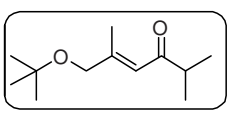
(*E*)-2-Methyl-1-(neopentyloxy)oct-2-en-4-one (46): colorless oil, 76% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 1H), 3.84 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 2.04 (s, 3H), 1.62 – 1.50 (m, 2H), 1.37 – 1.28 (m, 2H), 1.21 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 201.8, 154.3, 121.3, 73.7, 66.3, 44.3, 27.5, 26.3, 22.4, 16.6, 14.0. HRMS (ESI+): Calculated Mass for $C_{13}H_{25}O_2$ $[M+H]^+$: 213.1849, found: 213.1851.



(*E*)-4-(*Tert*-butoxy)-3-methyl-1-phenylbut-2-en-1-one (48): colorless oil, 64% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 6.9 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.45 (t, *J* = 7.4 Hz, 2H), 7.10 (s, 1H), 3.99 (s, 2H), 2.13 (s, 3H), 1.27 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ* 192.0, 156.4, 139.3, 132.4, 128.5, 128.3, 118.8, 73.8, 66.5, 27.6, 17.0. HRMS (ESI+): Calculated Mass for $C_{15}H_{21}O_2$ $[M+H]^+$: 233.1463, found: 233.1457.



(*E*)-6-(*Tert*-butoxy)-2,5-dimethylhex-4-en-3-one (50): pale yellow oil, 36% yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.42 (s, 1H), 3.86 (s, 2H), 2.73 – 2.56 (m, 1H), 2.04 (s, 3H), 1.21 (s, 9H). 1.08 (t, *J* = 5.3 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ* 205.3, 155.2, 120.2, 73.7, 66.4, 41.7, 27.6, 18.4, 16.7. HRMS (ESI+): Calculated Mass for $C_{12}H_{23}O_2^+$ $[M+H]^+$: 199.1693, found: 199.1694.



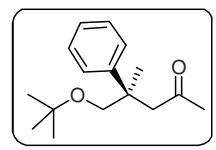
6.5.2 General procedure for the conjugate addition:

To a Schlenk tube equipped with a magnetic stirring bar and a septum was added palladium trifluoroacetate (8.3 mg, 5 mol%, 0.05 equiv), **L11** (9.6 mg, 7 mol%, 0.07 equiv) and arylboronic acid (1.5 mmol, 3 equiv). The Schlenk tube was capped and alternated through 3 cycles of vacuum evacuation and dinitrogen-backfill. The enone (0.5 mmol) was dissolved in 0.5 ml of 1,2-dichloroethane and added via a syringe. The walls of the Schlenk tube were washed with an additional 0.3 ml of the solvent. $KSbF_6$ (27.5 mg, 20 mol%, 0.2 equiv), dissolved in 0.2 ml of distilled water

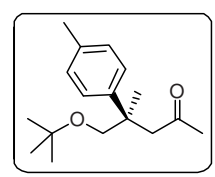
was added via syringe. The septum was replaced with a screw cap, under a positive pressure of dinitrogen and the reaction was placed in an preheated oil bath at 80 °C. Upon complete consumption of the enone (monitored by TLC / GC), the reaction mixture was allowed to cool to rt, and filtered through a pad of silica. The filtrate was dried over $MgSO_4$, concentrated in vacuo and adsorbed onto silica before being loaded on a silica-gel column. Elution with a mixture of pentane:ether afforded the corresponding product. *Note:* Water is immiscible with DCE, but this does not have an influence on the outcome of the reaction.

6.5.3 Characterization of the products

5-(*Tert*-butoxy)-4-methyl-4-phenylpentan-2-one (13): Synthesized according to the general procedure from **12** (0.5 mmol, 85 mg) and phenylboronic acid (1 mmol, 122 mg), and purified by flash chromatography (*n-pentane :* Et_2O = 20:1) to afford **13** (88 mg, 71%, 69% ee) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.36 (m, 2H), 7.35 – 7.30 (m, 2H), 7.25 – 7.18 (m, 1H), 3.52 (d, *J* = 8.5 Hz, 1H), 3.36 (d, *J* = 8.5 Hz, 1H), 2.92 (d, *J* = 15.5 Hz, 1H), 2.87 (d, *J* = 15.5 Hz, 1H), 1.92 (s, 3H), 1.44 (s, 3H), 1.15 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) *δ* 208.3, 146.0, 128.15, 128.14, 126.3, 126.1, 72.7, 69.6, 51.6, 41.3, 31.8, 27.4, 23.5. HRMS (ESI+): Calculated Mass for $C_{16}H_{25}O_2$ $[M+H]^+$: 249.1849, found: 249:1854. Chiral HPLC analysis, Chiralpak OJ-H column, *n*-heptane : *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 12.6 (minor) and 13.9 (major).

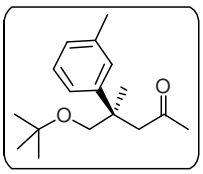


5-(*Tert*-butoxy)-4-methyl-4-(4-tolyl)pentan-2-one (13b): Synthesized according to the general procedure from **12** (0.5 mmol, 85 mg) and *p*-tolylboronic acid (1 mmol, 136 mg), and purified by flash chromatography (*n*-pentane : Et_2O = 20:1) to afford **13b** (97 mg, 74%) as a colorless oil. $[\alpha]_D^{20}$ = +2.4° ($CHCl_3$, *c* 0.33) for a 65% ee sample). ^{1}H-NMR (400 MHz, $CDCl_3$) δ. 7.23 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 3.45 (d, *J* = 8.5 Hz, 1H), 3.28 (d, *J* = 8.5 Hz, 1H), 2.83 (d, *J* = 2.7 Hz, 2H), 2.28 (s, 3H), 1.87 (s, 3H), 1.38 (s, 3H), 1.10 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 208.42, 142.96, 135.60, 128.87, 126.14, 72.65, 69.77, 51.72, 41.06, 31.89, 27.50, 23.50, 20.96. HRMS (ESI+): Calculated Mass for

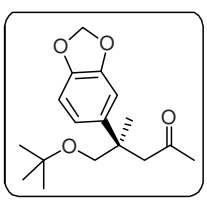


$C_{13}H_{17}O$ [M-O*t*Bu]$^+$: 189.1279, found: 189.1273. Chiral HPLC analysis, Chiralpak AD-H column, *n*-heptane : *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 10.9 (minor) and 11.4 (major).

5-(*Tert*-butoxy)-4-methyl-4-(3-tolyl)pentan-2-one (13c): Synthesized according to the general procedure from **12** (0.5 mmol,85 mg) and *m*-tolylboronic acid (1 mmol, 136 mg), and purified by flash chromatography (*n*-pentane *:* Et_2O = 20:1) to afford **13c** (92 mg, 70%) as a colorless oil. $[\alpha]_D^{20}$ = +3.6° ($CHCl_3$, *c* 0.55) for a 64% ee sample. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 3H), 6.96 – 6.94 (m, 1H), 3.43 (d, *J* = 8.5 Hz, 1H), 3.25 (d, *J* = 8.5 Hz, 1H), 2.28 (s, 3H), 2.83 (d, *J* = 2.7 Hz, 2H),1.84 (s, 3H), 1.35 (s, 3H),1.07 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ = 208.4, 145.9, 137.4, 127.9, 127.0, 126.8, 123.2, 72.6, 69.6, 51.6, 41.2, 31.8, 27.4, 23.4, 21.7. HRMS (ESI+): Calculated Mass for $C_{13}H_{17}O$ [M-O*t*Bu]$^+$: 189.1279, found: 189.1274. Chiral HPLC analysis, Chiralpak OJ-H column, *n*-heptane : *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 10.5 (major) and 10.9 (minor).

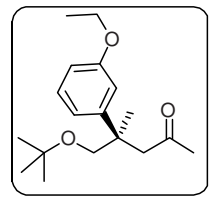


4-(Benzo[d][1,3]dioxol-5-yl)-5-(*tert*-butoxy)-4-methylpentan-2-one (13d): Synthesized according to the general procedure from **12** (0.5 mmol,85 mg) and 3,4-(methylenedioxy)phenylboronic acid (1 mmol, 166 mg) and purified by flash chromatography (*n*-pentane *:* Et_2O = 20:1) to afford **13d** (61 mg, 42% yield, 59% ee) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.93 (s, 2H), 3.42 (d, *J* = 8.5 Hz, 1H), 3.29 (d, *J* = 8.5 Hz, 1H), 2.82 (q, *J* = 15.6 Hz, 2H), 1.93 (s, 3H), 1.38 (s, 3H), 1.13 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 208.14, 147.42, 145.56, 140.04, 119.18, 107.73, 107.18, 100.81, 72.66, 69.84, 51.78, 41.12, 31.80, 27.40, 23.62. HRMS (ESI+): Calculated Mass for $C_{13}H_{15}O_3$ [M-O*t*Bu]$^+$: 219.1021, found: 219.1014. Chiral HPLC analysis, Chiralpak OJ-H column, *n*-heptane : *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 20.0 (minor) and 22.1 (major).

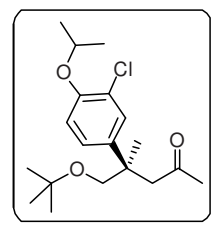


5-(*Tert*-butoxy)-4-(3-ethoxyphenyl)-4-methylpentan-2-one (13e): Synthesized according to the general procedure from **12** (0.5 mmol,85 mg) and 3-

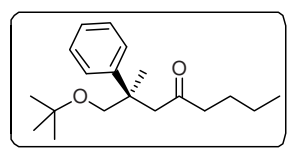
ethoxyphenylboronic acid (1 mmol, 166 mg) and purified by flash chromatography (*n*-pentane : Et_2O = 20:1) to afford **13e** (77 mg, 53% yield, 59% ee) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.23 (t, *J* = 9.3 Hz, 1H), 6.97 (d, *J* = 6.8 Hz,1H), 6.95 (s, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 4.03 (q, *J* = 7.0 Hz, 2H), 3.49 (d, *J* = 8.6 Hz, 1H), 3.33 (d, *J* = 8.5 Hz, 1H), 2.86 (s, 2H), 1.92 (s, 3H), 1.51 – 1.31 (m, 6H), 1.14 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 208.2 158.7, 147.7, 128.9, 118.6 113.6 111.3 72.6, 69.6, 63.3, 51.6, 41.4 31.8 27.4, 23.4, 14.9. HRMS (ESI+): Calculated Mass for $C_{14}H_{19}O_2$ [M-O*t*Bu]$^+$: 219.1385 found: 219.1379. Chiral HPLC analysis, Chiralpak OJ-H column, *n*-heptane : *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 21.5 (minor) and 22.1 (major).



5-(*Tert*-butoxy)-4-(3-chloro-4-isopropoxyphenyl)-4-methylpentan-2-one (13f): Synthesized according to the general procedure from from **12** (0.5 mmol, 85 mg) and 3-chloro-4-isopropoxyphenylboronic acid (1 mmol, 166 mg) and purified by flash chromatography (*n*-pentane *:* Et_2O = 20:1) to afford **13f** (141 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ = +3.6° ($CHCl_3$, *c* 0.24 for a 77% ee sample).^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.18 (d, *J* = 8.6 Hz,1H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.56 – 4.41 (m, 1H), 3.40 (d, *J* = 8.5 Hz, 1H), 3.31 (d, *J* = 8.5 Hz, 1H), 2.83 (q, *J* = 15.7 Hz, 2H), 1.95 (s, 3H),1.38 (s, 3H), 1.36 (d, *J* = 6.1 Hz, 6H), 1.13 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 207.9, 151.7, 139.5, 128.5, 125.4, 123.7, 115.5, 72.7, 72.1, 69.5, 51.4, 40.6, 31.8, 27.4, 23.3, 22.1, 15.3. HRMS (ESI+):Calculated Mass for $C_{15}H_{20}O_2Cl$ [M-O*t*Bu]$^+$: 267.1152, found: 267.1145. Chiral HPLC analysis, Chiralpak OJ-H column, *n*-heptane : *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 11.2 (minor) and 12.3 (major).

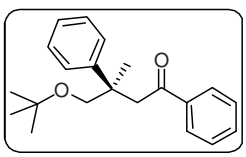


1-(*Tert*-butoxy)-2-methyl-2-phenyloctan-4-one (47): Synthesized according to the general procedure from (*E*)-2-methyl-1-(neopentyloxy)oct-2-en-4-one (**46**) (0.5 mmol,102 mg) and phenylboronic acid (1 mmol, 122 mg) and purified by flash chromatography (*n*-pentane : Et_2O = 20:1) to afford **47** (84 mg, 58%) as a colorless oil. $[\alpha]_D^{20}$ = +3.1° ($CHCl_3$, *c* 0.61) for 71% ee

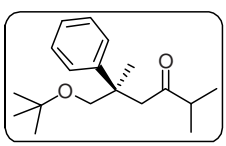


sample. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.35 (m, 2H), 7.32 – 7.28 (m, 2H), 7.23 – 7.15 (m, 1H), 3.52 (d, J = 8.5 Hz, 1H), 3.38 (d, J = 8.5 Hz, 1H), 2.94 – 2.79 (m, 2H), 2.86 (q, J = 22.3, 15.6 Hz, 2H), 1.44 (s, 3H), 1.43 – 1.36 (m, 2H), 1.23 – 1.15 (m, 2H), 1.14 (s, 9H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 210.3, 146.3, 128.1, 126.2, 126.1, 72.6, 69.5, 50.5, 44.2, 41.3, 27.5, 25.8, 23.5, 22.3, 13.9. HRMS (ESI+): Calculated Mass for $C_{15}H_{21}O$ [M-O*t*Bu]$^+$: 217.1592, found: 217.1589. Chiral HPLC analysis, Chiralpak OJ-H column, *n*-heptane: *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 8.6 (major) and 9.3 (minor).

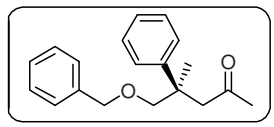
4-(*Tert*-butoxy)-3-methyl-1,3-diphenylbutan-1-one (49): Synthesized according to the general procedure from (*E*)-4-(*tert*-butoxy)-3-methyl-1-phenylbut-2-en-1-one (**48**) (0.5 mmol, 102 mg) and phenylboronic acid (1 mmol, 122 mg) and purified by flash chromatography (*n*-pentane *:* Et_2O = 20:1) to afford **49** (74 mg, 48%) as a colorless oil. $[\alpha]_D^{20}$ = +3.1° ($CHCl_3$, *c* 0.61 for a 69% ee sample).^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5, 8.1 Hz, 4H), 7.31 (t, J = 7.6, 8 Hz, 2H), 7.20 (t, J = 7.3 Hz, 1H), 3.62 (d, J = 8.5 Hz, 1H), 3.57 – 3.43 (m, 3H), 1.56 (s, 3H), 1.13 (s, 9H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 199.2, 146.7, 138.4, 132.6, 128.4, 128.1, 128.1, 126.2, 126.0, 72.7, 69.6, 65.9, 45.5, 41.6, 27.5, 23.9.



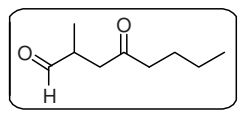
6-(*Tert*-butoxy)-2,5-dimethyl-5-phenylhexan-3-one (51): Synthesized according to the general procedure, from (*E*)-6-(*tert*-butoxy)-2,5-dimethylhex-4-en-3-one (**50**) (0.5 mmol, 102 mg) and phenylboronic acid (1 mmol, 122 mg) and purified by flash chromatography (*n*-pentane : Et_2O = 20:1) to afford **51** (44 mg, 32%) as a colorless oil. $[\alpha]_D^{20}$ = +2.3° ($CHCl_3$, *c* 0.43 for a 71% ee sample).^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.4 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.18 (t, J = 7.2 Hz, 1H), 3.53 (d, J = 8.4 Hz, 1H), 3.40 (d, J = 8.4 Hz, 1H), 2.92 (q, J = 16.5 Hz, 23, 2H), 2.44 – 2.41 (m, 1H), 1.44 (s, 3H), 1.13 (s, 9H), 0.97 (d, app. *t*, J = 7.9 Hz, 6H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 213.7, 146.6, 128.0, 126.2, 126.0, 113.8, 72.6, 69.3, 48.1, 41.7, 41.1, 27.6, 23.6, 18.2, 18.1. HRMS (ESI+): Calculated mass [M+Na]$^+$: 299.1987, found: 299.1983.



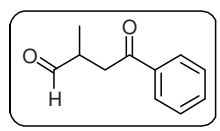
5-(Benzyloxy)-4-methyl-4-phenylpentan-2-one (53): Synthesized according to the general procedure, from (*E*)-5-(benzyloxy)-4-methylpent-3-en-2-one (0.5 mmol, 102 mg) and phenylboronic acid (1 mmol, 122 mg) and purified by flash chromatography (*n*-pentane : Et_2O = 20:1) to afford **53** (89 mg, 63%, 71% ee) as a colorless oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.15 (m, 10H), 4.53 (s, 2H), 3.69 (d, J = 8.9 Hz, 1H), 3.61 (d, J = 8.9 Hz, 1H), 2.94 (q, J = 15.5 Hz, 2H), 1.93 (s, 3H), 1.52 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 207.7, 145.3, 138.4, 128.3, 128.2, 127.5, 127.4, 126.3, 126.1, 78.0, 73.2, 51.5, 41.7, 31.8, 23.5. HRMS (ESI+): Calculated mass $[M+Na]^+$: 305.1512, found: 305.1511. Chiral HPLC analysis: Chiralpak AD-H column, *n*-heptane: *i*-PrOH 99:1, 40 °C, detection at 210 nm, retention times (min): 16.2 (minor) and 16.8 (major).



2-Methyl-4-oxooctanal (54): Isolated as a side product during the synthesis of **47**. Obtained as a colorless oil (26 mg, 33% yield).^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.67 (s, 1H), 2.95 – 2.84 (m, 3H), 2.46 – 2.39 (m, 2H), 1.60 – 1.52 (m, 2H), 1.37 – 1.26 (m, 2H), 1.13 (d, J = 7.3 Hz, 3H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 209.0, 203.5, 43.2, 42.9, 41.6, 26.0, 22.4, 13.9, 13.6. HRMS (ESI+): Calculated Mass for $C_{11}H_{13}O_2$ $[M+H]^+$: 157.1223, found: 157.1224.



2-Methyl-4-oxo-4-phenylbutanal (55): Isolated as a side product during the synthesis of **49.** Obtained as a colorless oil (26 mg, 30% yield) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 7.99 (d, J = 8.9 Hz, 2H), 7.57 (t, J = 7.4 Hz, 2H), 7.47 (t, J = 7.9 Hz, 1H), 3.49 (dd, J = 17.7, 6.5 Hz, 1H), 3.19 – 3.08 (m, 1H) 3.01 (dd, J = 17.7, 5.9 Hz, 1H), 1.25 (d, J = 7.3 Hz, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 203.5, 197.8, 136.7, 133.4, 128.7, 128.2, 41.7, 39.5, 13.9. HRMS (ESI+): Calculated Mass for $C_{11}H_{13}O_2$ $[M+H]^+$: 177.0910, found: 177.0909.



6.6 References.

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(2) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.

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